Association between early life cognitive activity and Alzheimer neurodegeneration in late life

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Association between early life cognitive activity and Alzheimer neurodegeneration in late life

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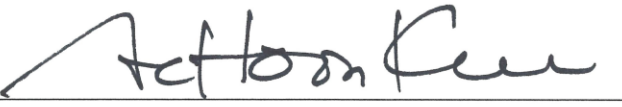

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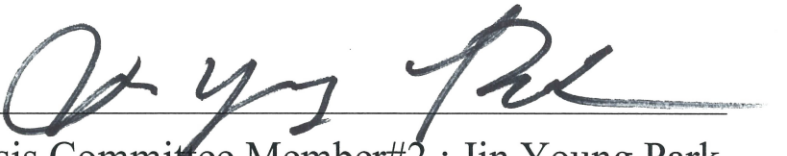

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ABSTRACT

Association between early life cognitive activity and Alzheimer neurodegeneration in late life

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Poor cognitive activity (CA) has been associated with cognitive decline and increased risk of Alzheimer's disease (AD) in elderly population. Although several studies investigated the relationship between current CA and AD pathologies including cerebral beta-amyloid (Aβ) deposition and AD-specific neurodegeneration, very little information is available for the association between CA during past lifetime periods and in vivo AD-related brain changes in the elderly. Among them, we focused early life including childhood and early adulthood, a critical period of brain development characterized by neural plasticity. We investigated the association between early life CA and AD-related neurodegeneration in non-demented elderly individuals.

Three-hundred twenty-one elderly individuals without dementia included from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study. All the subjects underwent comprehensive clinical and neuropsychological assessment and ^{18}F-fluorodeoxyglucose (FDG)-PET. We obtained participating frequencies of cognitive activity during early life by structured questionnaires. Multiple linear regression analysis was used across the whole cohort.

Of the 321 participants, 254 were cognitively normal (CN) and 67 had mild cognitive impairment. The mean age of participants was 69.6 years old (standard deviation [SD] = 8.0). Higher early life CA was associated with significantly increased cerebral metabolism of glucose of the AD-signature regions of interest (B = 0.035, SE = 0.013, P = .009).

Our results suggest that CA in early life may be protective against late life AD-related neurodegeneration. A cognitively active lifestyle in childhood and early adulthood needs to be more emphasized.

Key words : Cognitive activity, early life, Alzheimer's disease, neurodegeneration, beta amyloid

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I. INTRODUCTION

Past or current cognitive activity (CA) has been associated with reduced cognitive decline[1-4] or occurrence of Alzheimer's disease (AD) dementia[5-8] in non-demented old people. This suggests that cognitive activity is possibly associated with pathological process of AD. But information about how cognitive activity influence on ongoing AD process was limited.

AD process in the preclinical phase was stratified to three stages by the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease (NIA-AA). The first stage is asymptomatic amyloidosis and the second stage is evidence of synaptic dysfunction and/or early neurodegeneration as well as amyloid positivity. Third, and last stage is

initiating subtle cognitive decline caused by both of amyloid deposition and neurodegeneration.[9] About cerebral amyloid deposition starting from the first stage, several studies investigated association to lifetime CA itself or current and past CA and found association with amyloid deposition[10,11] or not.[12] About neurodegeneration including synaptic or neuronal dysfunction that become evident in the second stage, one study reported association between lifetime mental activity and reduced rate of hippocampal atrophy in small sample size.[13] However, current or past CA did not show association with neurodegeneration in later cross-sectional study with more sample size.[12,14] In short, most of previous studies focused on relationship between AD pathologies and overall lifetime CA or simply divided CA into current or past. The influence of certain life experiences, such as CA, on the brain may differ according to the stages of life.[4,11,15] Therefore, it would be limitation of the preceding investigations which did not take account into different life stages and it could be one of possible explanation for controversial results.

Especially, early life is critical period for brain development, and neural plasticity of this period could be possible mechanism of protective effect from cognitive activity.[16-18] One study proved association between higher early life CA and reduced longitudinal cognitive decline,[4] however, they defined early life until 40 years old. Another study explored about differential effect of age epochs on amyloid deposition.[11] However, as far as we know, no study directly investigated association between early life CA before second decades of life and

AD-related neurodegeneration. Previous findings about education which was mostly achieved in the early life reduced the age effect on AD related neurodegeneration biomarkers.[19] In the same vein, higher early life CA may associate with reduced AD-related neurodegeneration.

Therefore, we aimed to investigate the protective effect of early life CA on AD-related neurodegeneration in non-demented elderly individuals. We hypothesized that more frequent CA in early life, including childhood and early adulthood is associated with reduced neurodegeneration in old age by affecting brain change during development process.

To test the hypothesis, we used clinical and imaging data from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE). Participation frequency of CA was measured by structured questionnaires. AD-related neurodegeneration was measured by cerebral glucose metabolism using ^{18}F-fluorodeoxyglucose (FDG)-PET, previously described as reliable biomarker of neurodegeneration including neuronal/synaptic dysfunction which was related with AD.[9,20] We used regions of interest (ROI) of FDG-PET which were known to be sensitive measure of predicting AD related cognitive and functional decline.[21-23]

II. MATERIALS AND METHODS

1. Participants

This study was part of the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study, which began in 2014 and was designed to identify novel biomarkers for AD and explore various lifetime experiences contributing to AD-related brain changes. The current study included 321 community-dwelling elderly individuals without dementia who were at least 55 years old and enrolled between April 2014 and March 2016.

The study participants consisted of 254 cognitively normal (CN) and 67 mild cognitive impairment (MCI) subjects. All individuals with MCI met the current consensus criteria for amnestic MCI: 1) memory complaints confirmed by an informant; 2) objective memory impairment, 3) preserved global cognitive function; 4) independence in functional activities; and 5) no dementia. All MCI individuals had a global clinical dementia rating (CDR) of 0.5. In terms of Criterion 2, the age-, education-, and gender-adjusted z-scores for at least 1 of the 4 episodic memory tests was less than –1.0. The four memory tests included Word List Memory, Word List Recall, Word List Recognition, and Constructional Recall tests, which are included in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery. The CN group consisted of participants with a

global CDR of 0 and lack of an MCI or dementia diagnosis. The exclusion criteria were current serious medical, psychiatric, or neurological disorders that may influence mental functioning; the presence of severe communication problems that would hinder the clinical interview or brain imaging process; *in vivo* devices or a mental status that prevented us from performing the brain magnetic resonance imaging (MRI); absence of a reliable informant; illiteracy; participation in a different clinical trial; and treatment with an investigational product. The Institutional Review Board of the Seoul National University Hospital and Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center, South Korea, approved this study, and subjects and their legal representatives provided written consent.

2. Clinical assessment

All participants received standardized clinical assessments by trained psychiatrists based on the KBASE clinical assessment protocol, which incorporated the CERAD-K.[24] KBASE neuropsychological assessments incorporating the CERAD-K neuropsychological battery[25] were also administered to all participants by trained neuropsychologists.

3. Assessment of early life CA

Participant CA was assessed using a expanded version[7,15,26] of a previously reported 25-item autobiographical questionnaire,[10,27] which was shown to have

sufficient internal consistency and temporal stability. Items included relatively common activities with few barriers to participation, such as reading newspapers, magazines, or books; visiting a museum or library; attending a concert, play, or musical; writing letters; and playing games. Individuals completed the questionnaire at a baseline evaluation point. Frequency of participation was rated from 1 (once a year or less) to 5 (daily or approximately daily). There were 9 current (i.e., late life) activities and 30 previous activities including 11 related to childhood (6–12 years of age), 10 related to young adulthood (18 years of age), and 9 related to midlife (40 years of age). Item scores were averaged to yield separate values for each age period. The early life CA score was determined by averaging childhood and young adulthood scores.

4. FDG-PET acquisition and processing

Participants underwent FDG-PET imaging using a 3.0T Biograph mMR (PET-MR) scanner (Siemens, Washington DC, USA) according to the manufacturer's approved guidelines. The participants fasted for at least 6 hours and rested in a waiting room for 40 minutes prior to the scans after intravenous administration of 0.1mCi/Kg of [^{18}F]FDG radioligands. The following image processing steps were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2014a (Mathworks, Natick, MA, USA). First, static FDG-PET images were co-registered to individual T1 structural images and transformation parameters for the spatial normalization of individual T1 images

to a standard MNI template were calculated and used to spatially normalize the PET images to MNI template. After smoothing the spatially normalized FDG-PET images with a 12mm Gaussian filter, intensity normalization was performed using the pons as the reference region. Cerebral glucose metabolism of the AD-signature FDG ROIs (AD-CMglu) was defined as voxel-weighted mean standardized uptake value ratio (SUVR) values extracted from the AD-signature FDG ROIs (angular gyri, posterior cingulate cortex, and inferior temporal gyri) known to be sensitive measure of change in cognitive and functional status in MCI and AD patients.[21-23]

5. Statistical analysis

To examine participant characteristics, T-test and chi-square analysis was used. The association of early life CA (independent variable) with AD-CMglu (dependent variable) was examined using multiple linear regression analyses controlling for age, sex, and years of education as covariates in Model A and additionally controlling for cognitive status (CN or MCI) in Model B. All statistical analyses were conducted using SPSS Statistics version 23.0 (IBM Corporation, New York.) and clinical significance was defined as P value less than .05.

III. RESULTS

The demographics, CA variables, and baseline AD biomarker values of all the participants are shown in Table 1. The mean age of participants was 69.6 years old (standard deviation [SD] = 8.0) and mean years of education was 11.5 (SD = 4.7). Average cognitive activity participation frequency was 2.2 (SD = 0.7) in range with several times per year to several times per month. As shown in Model A, we observed significant positive association between early life CA and AD-CMglu after controlling for age, sex, education (Table 2 and Figure 1). Similarly, Model B showed positive association between early life CA and AD-CMglu after additionally controlling for current cognitive status (CN or MCI) (Table 2). Representative FDG-PET images comparison by high or low early life CA was shown in Figure 2.

Table 1. Participant characteristics

Characteristics	All participants
No. of study participants	321
Age, y	69.60 (7.99)
No. of females (%)	180 (56.07)
Education, y	11.54 (4.69)
MMSE score (maximum, 30)	25.92 (3.35)
GDS score (maximum, 30)	5.53 (5.33)
MCI, no. (%)	67 (20.87)
Early life CA score (maximum, 5)	2.24 (0.69)
AD-CMglu, SUVR	1.39 (0.13)

Key: MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; CA, cognitive activity; AD-CMglu, Alzheimer's disease signature region cerebral glucose metabolism; SUVR, standardized uptake value ratio;

Note: Data are presented as mean (SD) unless otherwise indicated.

Table 2. Multiple linear regression analysis showing the association between early life CA and AD-CMglu

	B	SE	β	*p*
Model A				
Age	-0.003	0.001	-0.182	.001
Sex	0.038	0.016	0.139	.02
Education	-0.005	0.002	-0.170	.02
Early life CA	**0.035**	**0.013**	**0.181**	**.009**
Model B				
Cognitive status[1]	-0.103	0.018	-0.311	<.001
Age	-0.002	0.001	-0.115	.04
Sex	0.023	0.016	0.085	.14
Education	-0.004	0.002	-0.151	.03
Early life CA	**0.026**	**0.013**	**0.135**	**.04**

Key: CA, cognitive activity; AD-CMglu, Alzheimer's disease signature region cerebral glucose metabolism;

[1] Cognitive status means current clinical diagnosis, CN or MCI.

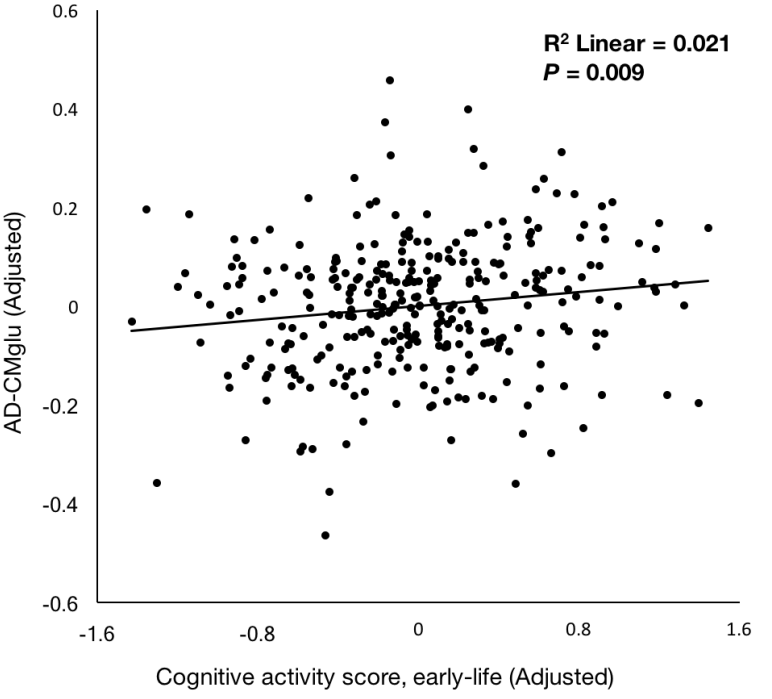
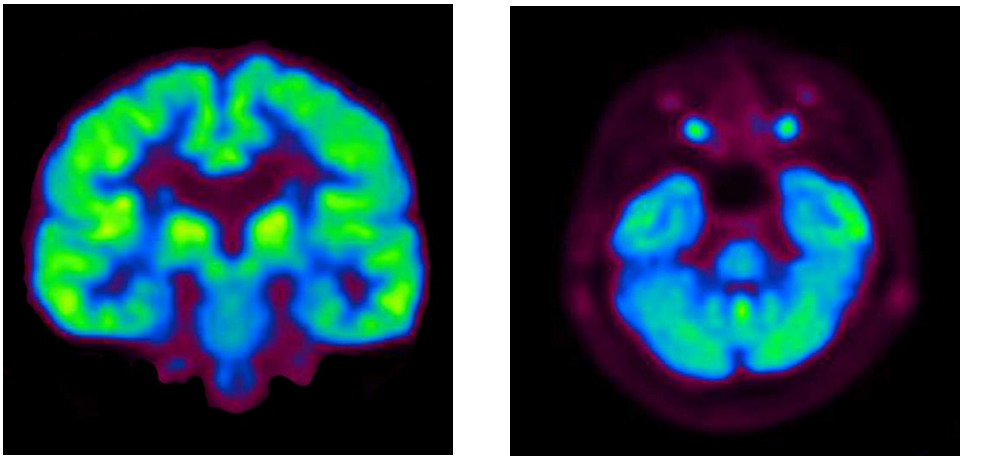


Figure 1. Partial regression plot showing the effect of early life CA on AD-CMglu.

Covariates included were age, sex and education. Early life CA was significantly associated with AD-CMglu (p = .009).

(A)



(B)

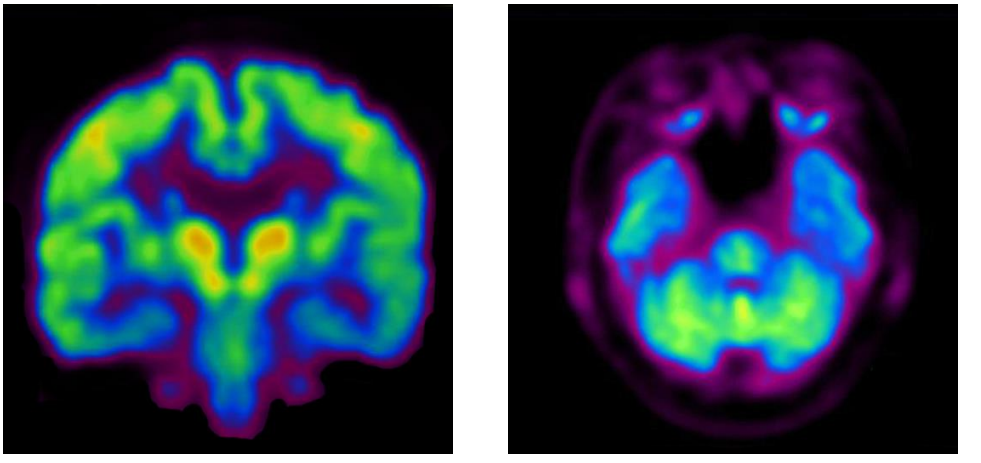


Figure 2. FDG-PET image showing difference of AD-CMglu by early life CA.

(A) Subject with high early life CA showed higher uptake (more brightness in image) in posterior cingulate and inferior temporal gyrus than pons as reference region, suggesting high SUVR in AD-signature FDG ROIs. (79 years old male, 16 years of education) (B) Subject with low early life CA showed almost similar uptake in posterior cingulate and inferior temporal gyrus with pons as reference region, suggesting low SUVR in AD-signature FDG ROIs. (77 years old male, 12 years of education)

IV. DISCUSSION

The results of this study support the hypothesis that early life CA was inversely associated with the degree of AD-related neurodegeneration in late life, suggestive of a potential mechanism underlying the inverse association between early life CA and AD dementia or cognitive decline. Several previous studies reported about importance of early life on cognitive function, such as childhood CA could reduce cognitive decline[4] and music or foreign language training in early life was associated with a lower risk of MCI or AD dementia.[28] Another study showed that a complex occupation could not compensate for low school grades at a young age to prevent dementia, suggesting relative importance of early life compared to mid- or late life, as critical period to build cognitive reserve against dementia.[18] However, to the best of our knowledge, no previous human studies have investigated the direct relationship between early life CA and AD-related neurodegeneration in late life.

The association between early life CA and AD-CMglu in late life may be explained by the influence of early life CA on brain developmental processes that continue until the second decade of life.[16,17,29,30] In particular, synaptogenesis and pruning proceed until the early adulthood period[31] and environmental enrichment could promote these processes, as shown in animal studies.[32,33] Other animal studies have shown that early life cognitive enrichment reduces memory deficits,[34] increases neurotrophic factors,[35] and

increases gene/protein expression related to synaptic plasticity.[36] It could be believed that early life CA promote synaptogenesis and/or pruning in humans, which manifest as changes in cerebral glucose metabolism until the second decade of life.[16] Therefore, early life CA probably increases synaptic density and/or function, which serves as a protective factor or neural reserve against neuronal dysfunction and/or other neurodegenerative changes in late life.

A previous report showed that higher-level education, related with early life enrichment, was associated with reduced age-related alterations of cerebrospinal fluid (CSF) neurodegeneration biomarkers (e.g., CSF total-tau, phosphorylated-tau), but not with amyloid biomarkers (CSF Aβ),[19] similar to our findings for early life CA and neurodegeneration. In our study, early life CA had a significant inverse relationship with AD-related neurodegeneration, even after controlling for the level of education. This finding suggests that early life CA itself is potentially protective against late life neurodegeneration or related cognitive decline, regardless of educational level.

Our results were different with recent two studies which measured CA and FDG-PET which showed no association between CA and AD-related neurodegeneration in non-demented individuals.[12,37] First study[12] used composite score consisting of current (late life) CA, education and occupation differently with our study only measured early life CA itself and controlled for education. Second study[37] was aimed to investigate the effect of midlife CA itself. Therefore, it could be explained by differential effect of age epochs

whether early life was included or not. Mid-to-late life has relative reduced brain plasticity compared with early life,[38,39] which means effect of CA on structural or functional brain change could be limited. Moreover, late life CA is inevitable for being affected by already accumulated AD pathology preceded to prominent cognitive impairment stage (reverse causality), such as Aβ burden, functional change like decreased cerebral glucose metabolism or more severely, structural change like cortical atrophy.[40] Reasons above would be potential confounding factor to find association between frequency of participating CA and brain changes in previous studies.

There are several limitations to our study. First, due to cross-sectional design, causality could not be precisely determined. Second, although we used well-validated and reliable questionnaires, retrospective measurements of CA may be influenced by recall bias. Current depression and memory impairment have the potential to affect retrospective measurements based on subjective recall. Despite our result still showed significant association between early life CA and FDG-PET value after controlling for cognitive status such as MCI could attenuate this concern, future long-term prospective studies are needed to confirm our findings. Second, as AD-related neurodegeneration measure, we used FDG-PET alone. Although we defined AD-CMglu by applying AD-signature ROIs reflecting typical AD-pattern hypometabolism, glucose metabolism may be influenced by non-AD pathologies, such as vascular pathology and non-AD degenerative conditions.[41] Combining other

neurodegeneration biomarker of AD such as hippocampal volume, cortical thickness measured by structural MRI[42] or in vivo tau level measured by PET[43] as more AD-pathology specific biomarker may provide valuable information to address this issue. Last, we measured CA by quantitative measure like participating frequency, qualitative approach to measure cognitive activity would be one of the future direction of investigation.

V. CONCLUSION

In conclusion, our results support that CA in early life is probably protective against late life AD-related neurodegeneration. With respect to prevention of dementia and cognitive impairment in late life, a cognitively active lifestyle in childhood and early adulthood needs to be more emphasized.

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ABSTRACT(IN KOREAN)

생애 초기 인지 활동과 알츠하이머 신경퇴행의 연관성

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고 강

낮은 인지 활동 (Cognitive activity, CA) 참여도는 노인 인구에서 인지 저하와 알츠하이머병 (Alzheimer's disease, AD) 발병 위험을 높인다고 알려져 있다. 비록 몇몇 선행 연구에서 현재, 또는 과거의 인지 활동과 베타-아밀로이드 축적, 신경퇴행 등과 같은 알츠하이머병 관련 병리의 연관성을 조사한 바 있으나 아직까지 일관된 결과는 보고된 바가 없는데, 이러한 결과에 영향을 미치는 요인 중 하나로 인지 활동 참여 시기에 따라 인지 활동이 뇌에 미치는 영향이 달라질 수 있다는 것을 들 수 있겠다. 따라서 본 연구에서는 전체 생애 주기 중에서 뇌 발달이 주로 이루어지고 신경 가소성이 높은 생애 초기에 초점을 맞추어 생애 초기 인지 활동과 알츠하이머병 관련 신경퇴행 (AD-related neurodegeneration) 간의 관계를 비치매 노인을 대상으로 조사하였다.

연구 대상자로는 현재 진행중인 한국인 뇌 노화 연구 (Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's disease, KBASE) 참여자 중 임상 및 신경심리 평가, 구조화된 설문지를 통한 인지 활동 참여도 평가, 그리고 ^{18}F-fluorodeoxyglucose (FDG)-PET 검사를 완료한 321명을 포함하였고 인지 활동과 AD 특이 부위의 뇌 포도당 대사 간의 연관 관계를 확인하기 위하여 다중 선형 회귀 분석을 시행하였다.

대상자들 중 254명은 정상 인지 노인, 67명은 경도인지장애로 진단되었으며 참여자들의 평균 연령은 69.6세 (표준 편차 = 8.0) 였다. 다중 선형 회귀 분석 결과, 생애 초기의 인지 활동 참여가 높을수록 AD와 관련된 뇌 영역의 포도당 대사가 증가함을 확인할 수 있었다 (B = 0.035, SE = 0.013, P = 0.009).

본 연구 결과는 생애 초기의 인지 활동이 노년기의 알츠하이머병 관련 신경퇴행의 감소와 연관이 있음을 시사하며 알츠하이머병 예방 측면에서 생애 초기부터 인지 활동에 활발히 참여하는 것이 중요함을 확인하였다는 데 의의를 갖는다.

핵심되는 말 : 인지 활동, 생애 초기, 알츠하이머병, 신경퇴행, 베타-아밀로이드